Prospective study on aflibercept to treat PEDs secondary to nAMD

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Age-related macular degeneration (AMD) is one of the leading causes of blindness. Pigment epithelial detachments (PED) can accompany neovascular AMD (nAMD) in as many as 62% of patients. PEDs are thought to be formed by the accumulation of fluid, blood, drusenoid material or fibrovascular tissue, which separates the retinal pigment epithelium from Bruch’s membrane. Anti-VEGF treatment has become the mainstay of treatment for neovascular AMD. However, there is a paucity in the literature on the effects of aflibercept on PEDs secondary to nAMD. In this issue, Diaconita et al. (2019) report on their prospective, exploratory, open-label study aimed at understanding the effects of intravitreal aflibercept in treating patients with PED secondary to nAMD. The authors recruited 36 patients (37 eyes) who were ≥55 years of age with PEDs secondary to nAMD and no previous anti-VEGF injections. Patients were injected with 2 mg of aflibercept on a monthly basis for three months followed by bimonthly injections for another nine months. Measures of patients’ vision-related quality of life and best corrected visual acuity (BCVA), ophthalmic examinations, optical coherence tomography (OCT), and fluorescein angiography (FA) were performed on a regular basis. Indocyanine green (ICG) studies were also performed at baseline, 4 month, and 12 months. In addition to the study schedule, patients also received injections when needed in the case of disease progression or recurrence. Patients were classified into two categories based on OCT changes at 4 months: responders (OCT reduction of PED size ≥ 25%) or partial responders (OCT measured reduction of PED size < 25%).

Of the 37 eyes included in the study, 27 (73.0%) were responders to aflibercept injections. The authors showed that PED height reduction was significantly different even after receiving one injection when comparing responders to partial responders. On average at 2 months (after 1 injection), PED height was 336.5 μm in responders compared with 63.9 μm in partial responders and at 12 months, PED height reduction was 348.6 μm in responders vs. 94.5 μm in partial responders. Similarly, after 12 months of injections, the BCVA of patients had an average gain of 10.1 ETDRS letters, with 14.0 letters in responders versus 0.5 letters in partial responders. At the end of one year, complete resolution of the PED was achieved in about one-third (32.3%) of patients. One patient, who had the largest PED (1009 μm), suffered a retinal tear, otherwise there were no other complications.

Similar to the current study, previous retrospective studies have also shown a decrease in PED height after aflibercept use. Furthermore, two prospective studies showed a reduction in PED size when patients were switched to aflibercept after failing ranibizumab treatment. In addition to the decrease in PED height, Diaconita et al. found significant vision gain in patients receiving aflibercept. As noted by the authors, some of the limitations of this study include small sample size and lack of control group. Overall, the study provides valuable evidence for the use of aflibercept in the treatment of nAMD associated PEDs, and it suggests that patients who show good initial response (responders) after 3 injections will likely have significantly better final outcomes compared with patients who do not show much improvement (partial responders). However, further studies are required to better understand treatment response.

Clinical practice point: Aflibercept shows significant promise in the improvement of visual acuity and reduction of PED height in the setting of nAMD. Patients who show good OCT response through the reduction of PED height after the first couple of injections of aflibercept will likely have better final outcomes compared with patients who do not respond initially.

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Identifying a retrobulbar hematoma on orbital imaging: should we worry?

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A retrobulbar hemorrhage is an uncommon yet potentially sight-threatening complication following orbital trauma or surgery. If the hemorrhage or associated orbital edema leads to an acute rise in orbital pressure, a compartment syndrome can develop and compromise perfusion to the retina and optic nerve. A large study described a remaining visual acuity of 20/100 or worse in over a third of patients with orbital compartment syndrome, even despite successful canthotomy and cantholysis procedures. The importance of remaining vigilant about the possibility of raised orbital pressure is highlighted by a short 1- to 2-hour interval following trauma where intervention might be effective in restoring vision.

While strategies for intervening in cases of suspected orbital compartment syndrome have been well described, there is little guidance on how to manage a retrobulbar hemorrhage identified on orbital imaging. In this issue, Kondoff et al. eloquently address this knowledge gap. The authors conducted a 3-year retrospective review of 256 patients with orbital fractures referred for an ophthalmic assessment. Retrobulbar hemorrhages were identified in nearly one-third of all cases of orbital fractures imaged by computed tomography (CT) of the facial bones. Of these cases, however, only one developed a clinical orbital compartment syndrome and required urgent medical and surgical intervention. In addition, of those patients where follow-up data was available, none of those with CT evidence of retrobulbar hemorrhage went on to later develop orbital compartment syndrome. As a result, the authors conclude that a retrobulbar hemorrhage identified radiographically, in the absence of other clinical findings, is unlikely to develop into a sight-threatening orbital compartment syndrome.

Given the urgency in diagnosing an orbital compartment syndrome, exploring how to approach the radiographic finding of retrobulbar hemorrhage has significant clinical importance. The nearly one-third of fracture cases associated with orbital hemorrhage identified in this study, however, is surprisingly high. This may be explained by the authors using cases from a database of patients who required close follow-up. In support of this, a previous study did not identify a retrobulbar hemorrhage in 65 cases referred with orbital fracture. Nevertheless, the question of how to manage a radiographic finding of a retrobulbar hemorrhage in this setting is not uncommon. Knowing that approximately 1% of these cases develop orbital compartment syndrome is very useful and further supports raised orbital pressure being a clinical diagnosis.

Finally, by exploring factors associating orbital fractures with retrobulbar hemorrhage, the possibility exists for classifying a type of fracture or hemorrhage as higher or lower risk for developing orbital compartment syndrome. Despite the low frequency of orbital compartment syndrome in radiographically identified retrobulbar hemorrhage in general, clinical features such as fracture location, anticoagulation use, and hematoma size may be important in guiding how closely these patients need to be followed.

In summary, Kondoff et al. have provided evidence that a retrobulbar hemorrhage identified on CT imaging is not very specific for raised orbital pressure in patients with an orbital fracture. This finding reassures practitioners that orbital compartment syndrome remains a clinical diagnosis.

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False negative results do occur, which is largely attributed to lamina, intimal hyperplasia and multinucleated giant cells.

2. Fattahi T, Brewer K, Retana A, Ogledzki M. Incidence of retrobulbar pathology in temporal artery biopsies

There has been increasing interest in diagnosis of GCA using non-invasive imaging techniques. MRI and MR angiography allow for simultaneous visualization of the bilateral temporal arteries as well as extra- and intracranial vessels with high sensitivity and specificity for GCA. A recent meta-analysis of the use of temporal artery ultrasound in GCA reported sensitivity and specificity of 68% and 81% respectively for a hypoechoic “halo sign.” The current study highlights the importance of tissue diagnosis, as not all inflammatory changes detected through imaging of the temporal arteries will be due to GCA. It is important to distinguish between GCA and other forms of vasculitis as the organ system involvement, prognosis and management differ.

Biopsy findings led to a change in management in several of the cases described in the current work. In addition, isolated small vessel changes are unlikely to be captured using these imaging modalities. Although GCA is classically described as a medium- and large-vessel vasculitis, small vessel vasculitis is present in most temporal artery biopsy specimens and, as in the current study, may be the only histological evidence of inflammatory pathology.

One limitation of this work is that it is not clear whether the clinical picture for each patient was consistent with GCA, or whether the patients with alternate diagnoses after biopsy had displayed features suggestive of other etiologies that were missed. The importance of history and physical examination in the work-up of vasculitis must not be underestimated. The initial diagnosis of GCA and decision to initiate steroid treatment must be made based on clinical assessment as one cannot afford to wait for biopsy results and risk permanent vision loss or other serious complications.

Given the variability in the extent and type of arteritis produced by this condition, there will always be patients diagnosed as “biopsy-negative GCA.” However, it would certainly be prudent to do everything possible to maximize yield of a temporal artery biopsy. The results of the current study taken together with the literature evidence for isolated small vessel disease in GCA strongly suggests that when biopsy is indicated, inclusion of periadventitial tissue should be the standard for submitting temporal artery specimens. This would be particularly important in cases where clinical presentation is unclear, or not classic for GCA.

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A resident’s perspective on tube shunt surgery in pig eyes: wet lab teaching model
Jessica Ruzicki, PGY-5

Participating in surgeries can be one of the most exciting times during ophthalmology residency, but also one of the most daunting. In my experience, preparation is a key component of any successful procedure. Several modalities are commonly used to introduce, develop and maximize surgical skills and techniques. As residents, we primarily rely on reading literature, attending didactic teaching, reviewing surgical videos, observing live surgeries, and ultimately performing surgeries on patients. However, as research and technological developments advance surgical techniques, the use of the wet lab to acquire and practice new skills is increasingly important to residents.

For example, glaucoma has recently seen a shift in surgical practice patterns. In Seven- and eight-year trends in resident and fellow glaucoma surgical experience, Chadha et al. acknowledge a decline in the average number of primary filtering surgeries by 20%, with a parallel increase in average primary glaucoma drainage implant surgeries by 40%, during 2009 to 2016.1 In this issue, Plemel et al. designed a wet lab model to teach the techniques for tube shunt surgery using freshly enucleated pig eyes.2

The study evaluated 6 ophthalmology trainees with experience ranging from PGY-1 to PGY-5. These residents prepared for their wet-lab session by reading the indications and complications of the surgery, watching videos outlining the applicable technique and were guided through a didactic session on the topic. Finally, fellowship-trained glaucoma specialists supervised and provided feedback during a three-hour wet lab. Post teaching, Plemel et al. identify a statistically significant improvement in the self-reported mean comfort level for the residents performing each skill associated with the procedure.

Although wet labs are useful tools for learners, the authors also note some drawbacks in this instance. Specifically, they discuss several differences between porcine eyes and human eyes, which include thin, stiff, friable and adherent conjunctiva, difficulty with burying knots in the sclera, a shallow anterior chamber, a thicker cornea and an overall lack of expected bleeding. They acknowledge that the many differences of a porcine eye may not result in a direct correlation to expected bleeding. They acknowledge that the many differences of a porcine eye may not result in a direct correlation to increased comfort in performing the live surgery. With respect to their study, Plemel et al. also observe that their sample size was small and from their home institution, and finally that there was a lack of a control group for comparison sake, which may necessitate improvements to future studies.

In summary, Plemel et al. demonstrated that creating a structured wet lab allows trainees to practice and optimize the required surgical skills for the newer aqueous tube shunt procedures. As noted, there can be limitations on the experience gained in a wet lab setting, however, I would certainly recognize that shifts in surgical techniques require additional exposure and practice opportunities for residents to best prepare for live surgeries.

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References
Resident Perspective: a semi-automated platform for pixel-based quantification of choroidal naevus progression

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Choroidal nevi are common, benign, melanocytic intraocular tumours that tend to be flat or minimally elevated and occur most often in the post-equatorial fundus. Around three quarters are pigmented (melanotic). Their prevalence is estimated to be 5% among adults 40 years of age or older in the general U.S. population. Although benign, they carry a small risk of transformation into malignant melanoma. Assuming that one in five choroidal melanomas develop from a nevus, the lifetime risk of malignant transformation in the US population has been estimated to be 0.2%.  

Tumour growth is a feature of malignant transformation and one of the strongest predictors of metastatic spread. Early detection of transformation, with prompt treatment, improves prognosis. Clinical factors predictive of nevus growth can be remembered using the mnemonic: To Find Small Ocular Melanoma (Thickness >2mm, presence of subretinal Fluid, Symptoms of flashes, floaters or blurred vision, Orange pigment on the tumour surface, and tumour Margin ≤ 3mm from the optic nerve, http://www.ocularmelanomacalculator.com/).  

It is recommended that nevi without the above high-risk features be evaluated annually for evidence of malignant change. The current standard of care involves surveillance using serial colour fundus photographs. In this issue, Bontzos and colleagues evaluated a semi-automated method to aid in detecting nevus growth. Their method uses an open-source image analysis software (ImageJ, https://imagej.nih.gov/ij/) to segment nevi from background based on thresholds of colour saturation, intensity and hue, thereby estimating the area occupied by the nevi.  

From a test-retest analysis of 25 pairs of fundus photographs obtained at the same visit, they estimated that their method is reliable in detecting changes in nevus area of ≥ 0.7mm². Applied to photographs from a sample of 87 eyes of 87 people followed annually for 5 years, their method had 50% greater sensitivity and 100% specificity for detecting nevus progression compared to standard photographic assessment by two independent ophthalmologists. Bontzos and colleagues’ method may prove to be a useful aid for detecting nevus growth, but it remains to be determined what amount or rate of change in nevus surface area suggests malignant change. Previous research has found that 30% of nevi enlarge without evidence of transformation. Fortunately, an expanding array of imaging modalities is available to assist in distinguishing malignant from benign melanocytic tumours, including ultrasonography, enhanced depth optical coherence tomography, fundus autofluorescence, and optical coherence tomography angiography.  

References

Current and future applications of optical coherence tomography angiography in diabetic retinopathy

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Optical coherence tomography angiography (OCTA) is a noninvasive imaging technique that provides quantitative information about vessel density and blood flow within the retina and choroid. Through repeated B-scans, variations in reflectivity, phase shift, or phase variance can be used to create microvascular flow maps. Flow maps from different segmentation slabs can be obtained, which include the superficial capillary plexus (SCP), intermediate capillary plexus (ICP), deep capillary plexus (DCP), and choriocapillaris slabs. Two general OCTA scanning methods are available in the form of spectral-domain (SD) and swept-source (SS) technology that differ in the type of light source and detector used. SS technology allows for higher scanning speeds and greater light penetration into deeper tissues such as the choroid and choriocapillaris.

The hallmark of diabetic retinopathy (DR) is vascular changes that involve different retinal layers. While fluorescein angiography (FA) is the criterion standard for evaluating retinal blood flow, it is invasive, time-consuming, and FA images can be obscured by fluorescein leakage. In this issue, Akil et al. review the utility of OCTA for patients with DR, including its role in DR screening, monitoring, and treatment guidance.

DR is the most common cause of legal blindness in the working-age population and the leading cause of visual impairment in Canada. Identifying those at high risk of developing DR may help to reduce its sight-threatening complications and blindness. Before the development of clinically detectable DR, OCTA may reveal changes in the retinal microvasculature. Changes in foveal avascular zone (FAZ) parameters can be used as a measure of macular ischemia, which has been associated with functional damage and DR progression. Enlargement and loss of circularity of the FAZ on OCTA have been reported to correlate with increasing DR severity.

In monitoring DR, diabetic macular ischemia (DMI) has been identified as a risk factor for disease progression. Macular perfusion is often evaluated by vessel density and OCTA enables mapping of retinal perfusion impairment through color-coded perfusion density mapping.

OCTA is also particularly useful in guiding treatment. Further delineation of the microvascular structure enables characterization of intraretinal microvascular abnormalities (IRMA) by their branching patterns. This allows improved identification of IRMA at risk of neovascular progression. Neovascular growth and branching complexity in proliferative diabetic retinopathy (PDR) and microaneurysm characterization in relation to the presence of diabetic macular edema (DME) can also be evaluated by OCTA, which may facilitate treatment decisions as well.

OCTA is valuable in providing information about capillary networks in different slabs and areas obscured by fluorescein leakage in FA images. This is both clinically relevant and adds to the current knowledge surrounding DR pathogenesis. However, OCTA technology is fairly new and as such, has its limitations. It is limited in its ability to provide information about blood flow velocity or volume and has a limited field of view of 70 degrees at best. Furthermore, quantification of microvascular structure and flow is highly dependent on image quality—OCTA can be limited by imaging artifacts, especially when analyzing deep retinal vascular networks. Akil et al. comment that while OCTA provides additional information about capillary integrity, the technology at its current stage cannot replace FA, fundus biomicroscopy, or ultra-wide field fundus photography in clinical practice. Faster OCTA devices, improved algorithms to resolve image...
processing issues, and reliable databases of OCTA biomarkers are needed to enhance more widespread adoption in the future.

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